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Case report

Focal sensory-motor status epilepticus in multiple sclerosis due to a new cortical lesion. An EEG–fMRI co-registration study

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ABSTRACT

A case of focal inferior limb sensory-motor status epilepticus as the only manifestation of a multiple sclerosis (MS) relapse is described. To obtain evidence of the relationship between the seizures, the cortical plaque and the left foot motor area, an EEG–fMRI co-registration study was undertaken demonstrating that seizure-related BOLD signal substantially overlapped with the inflammatory lesion involving the foot sensory-motor cortex. Seizures did not respond to intravenous anti-epileptic drugs (AEDs) but were controlled by steroid therapy.

1. Introduction

Epilepsy prevalence in Multiple Sclerosis (MS) patients is significantly larger that in general population, ranging from 2% to 5%.[1,2] Epilepsy, associated with other symptoms, may affect patients during early and chronic phases of the disease. However, a causative link is difficult to establish as many of earlier studies neither mention the diagnostic criteria used to classify affected patients, nor they provide detailed description of seizures and clear anatomo-electroclinical correlations between ictal semiology and imaging.[2] There has also been confusion between epilepsy and non-epileptic paroxysmal tonic fits arising from brainstem or spinal lesions.[3] Despite these considerations, there is a small group of patients in which a causal association between MS and epileptic seizures has been demonstrated.[4–8] Rarely, seizures have been described as the only manifestation of a disease relapse.[4–6]

We describe a patient suffering from clinically defined MS in which focal sensory-motor status was the only manifestation of a disease relapse due to a new small intra-cortical plaque. An extensive neurophysiological and multimodal fMRI study was performed to establish the causative role of the cortical lesion.

2. Case report

The patient was a 42-year old man with a 13-year history of MS and minimal disability (Kurtzke's Expanded Disability Status Scale = 1). A previous diagnosis of relapsing-remitting MS was formulated according to McDonald's criteria.[9] CSF examination demonstrated oligoclonal bands. Patient's last disease relapse (right limbs sensory deficit and weakness) dated 1-year back.

One month before presentation, the patient began complaining paroxysmal attacks lasting seconds to minutes characterized by stiffness and jerks of the left leg. Frequency and duration of these episodes progressively increased up to 20–40 attacks/day finally evolving into two generalized tonic–clonic convulsions. At admission paroxysmal motor events were characterized by involuntary contraction of the left foot with a dystonic attitude, followed by clonic leg movements. The attacks occurred at rest every 10–15 min and they could also be triggered by tactile stimuli applied to the sole of the left foot and by voluntary or passive movements of the left foot.

To ascertain the epileptic origin of the patient's fits, we performed a video-polygraphic recording (Fig. 1): 24 events were observed. Interictal EEG showed the presence of theta activities and sharp waves at the vertex region. A rhythmic poly-spikes discharge was observed in association with left tibialis anterior muscle tonic–clonic contraction.

The patient underwent brain MRI (3-T Philips) that showed the presence of one small non-enhancing intra-cortical lesion in the right paracentral lobule, that was absent in a 3 months earlier brain

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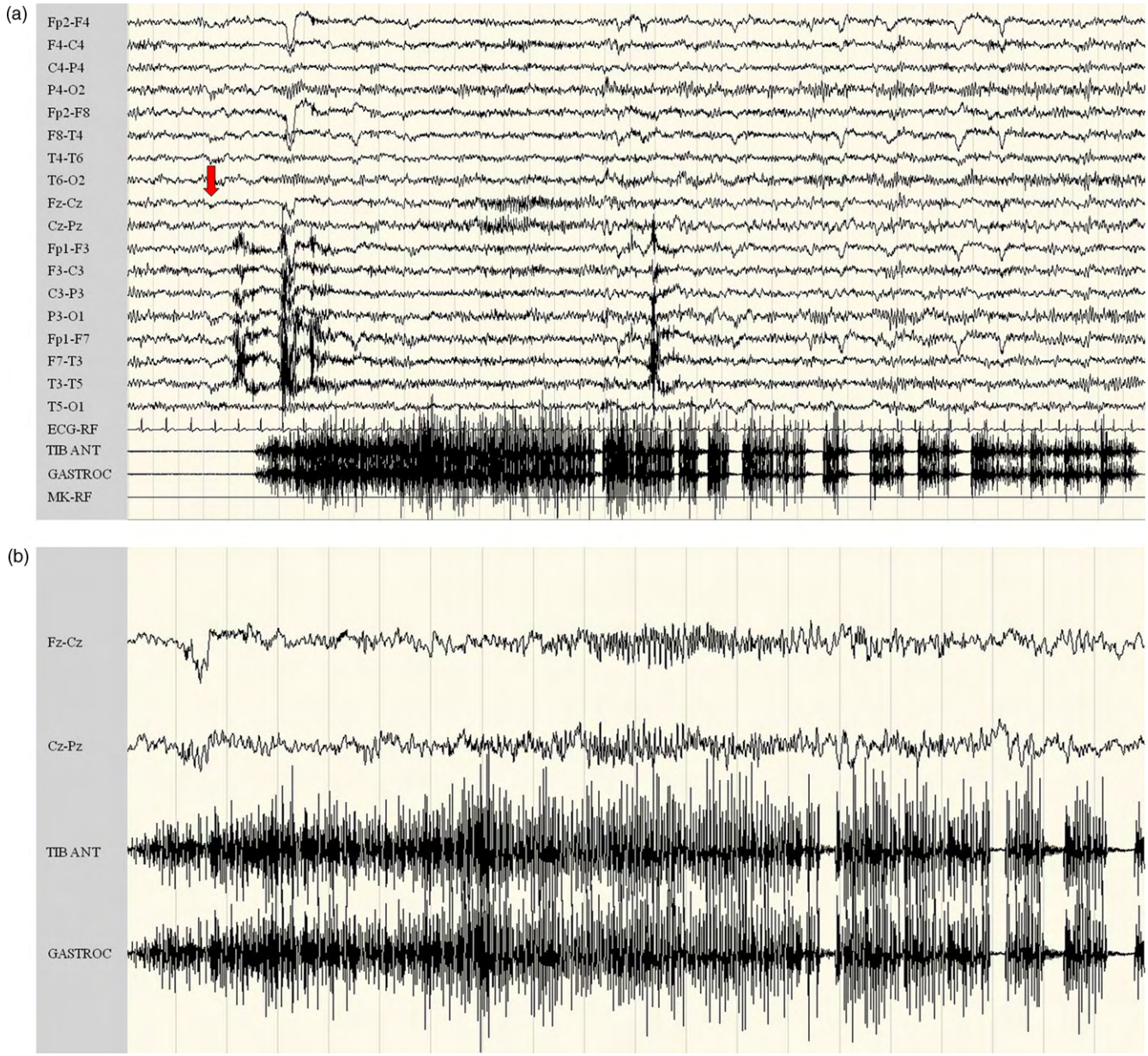

Fig. 1. Video-polygraphic monitoring: low-voltage de-synchronization of EEG activity (red arrow) precede the EMG tonic activity. Then the tonic muscle contraction is associated with fast rhythmic discharge at the vertex region. Finally, the clonic phase of left Tibialis anterior muscle contraction is associated with theta activity in the same EEG derivation (b detail of a). The EEG trace does not show a clear spikes discharge at the onset of the EMG activity in accordance with the deeply location of the epileptogenic zone in the medial surface of the frontal lobe. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

MRI performed as standard 1-year imaging follow-up in MS patients at our clinic (Fig. 2).

3. Multimodal functional MRI study

To map the relationship between the seizures, the cortical plaque and the left foot motor area, the patient underwent an EEG–fMRI co-registration of ictal seizure activity as well as a fMRI mapping of the foot motor and somato-sensory area. The study was performed when patient's seizures were characterized by only a focal dystonic contraction of the foot with no other overt movement. At this time seizures were not triggered by movement but occurred after tactile stimulation of the sole of the foot.

Simultaneous co-registration of EEG and fMRI enables identifying changes in cerebral blood oxygenation level-dependent (BOLD) signal related to specific EEG events, combining temporal resolution of EEG with spatial resolution of fMRI. Scalp EEG was recorded by means of a 32 channels MRI-compatible EEG recording system (Micromed, Italy). To remove pulse and movement artifacts during scanning two of these electrodes were used to record the electrocardiogram (ECG) and electromyogram (EMG). The EMG electrode was placed on the right abductor pollicis brevis muscle.

Functional data were acquired with a 3T Philips Achieva MR system. Each BOLD-echoplanar volume consisted of 30 transverse slices (TR = 3000 ms; 64×64 in plane matrix; voxel size 4 mm $\times$ 4 mm $\times$ 4 mm). In addition, at the end of the functional session a high-resolution T1-weighted image of the brain was acquired to allow anatomical localization of activations. The volume consisted of 170 sagittal slices (TR, 9.9 ms; TE, 4.6 ms; voxel size, 1 mm $\times$ 1 mm $\times$ 1 mm).

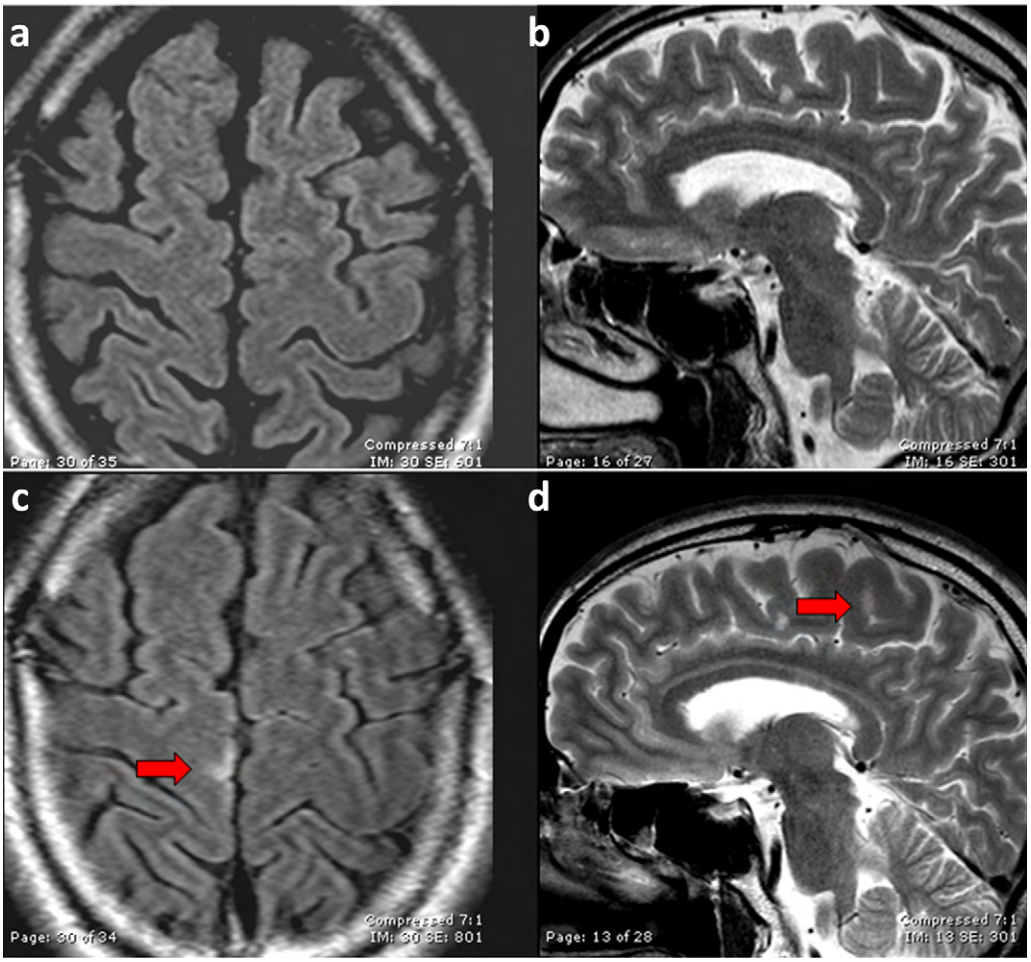

Fig. 2. MRI pre- (a and b) and post- (c and d) disease relapse (axial FLAIR and saggital T2-weighted images). The two exams (at a 3 months interval) were acquired with the same sequence protocol and with the same 3-T Philips Achieva scan. A new small intra-cortical lesion was evident in the right paracentral lobule (c and d – red arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

The patient underwent three 10-min fMRI recordings: 119 volumes were collected in each scanning session. To map reflex seizures an event-related data analysis was conducted on 3 events versus rest (brief electrographic seizures induced by foot somato-sensory stimulation); the EEG artifact induced by the magnetic field gradient was digitally removed off-line using an adaptive filter (Micromed). Then the filtered EEG was reviewed and the time of onset and duration of each electrographic seizure was marked. To map the somato-sensory cortex an event-related analysis was conducted on 6 events (tactile foot somato-sensory stimulation without seizures compared versus rest). Each event was convolved with the standard hemodynamic response function (HRF). To map the foot motor area a blocked design was used to compare periods of foot dorsi-flexion versus rest.

fMRI data analysis was performed with SPM5 software (Wellcome Department of Imaging Neuroscience). A *t*-statistic was used to determine significance on a voxel-by-voxel basis and correlation values were transformed into a normal distribution (*Z*-statistic). We identified the single region of condition-associated BOLD signal changes with a statistical threshold based on the amplitude ($p < .05$, corrected for multiple comparisons).

fMRI results showed overlapping clusters for both the motor and the somato-sensory stimulation located in the paracentral lobule and surrounding the intra-cortical plaque. Moreover, increased BOLD signal due to reflex seizures substantially overlapped with the cortical regions activated during voluntary foot movement and somato-sensory stimulation (Fig. 3). No cluster of deactivations (BOLD signals decreases versus the resting condition) was observed near the lesion nor at distant localizations.

4. Treatment and follow-up

The patient was initially treated with i.v. diazepam (10 mg): the seizure stopped but soon recurred after 30 min. We then administered i.v. phenitoin (1000 mg bolus followed by 750 mg/die) with serum concentration in the therapeutic range on the second day of treatment. However, there was no change in seizure frequency within the next 3 days, albeit seizures intensity and duration was shorter. Steroid therapy i.v. (1000 mg metil-prednisolone) was then started with a marked seizures reduction. Seizures were completely controlled after 5 days of steroid treatment. At discharge no anti-epileptic drug (AED) was prescribed to the patient. At 30-day and 3-month follow-up seizures did not recur. Video-polygraphic recording showed no evidence of subclinical seizures or minor motor events such as myoclonus. However, at 6 months of follow-up the patient complained of occasional tonic–clonic seizures of the left leg. A new brain MRI did not reveal new lesions and the patient was scheduled with oral phenitoin (200 mg die) with complete seizure control. At 1-year follow-up the patient is seizure free on phenitoin 200 mg.

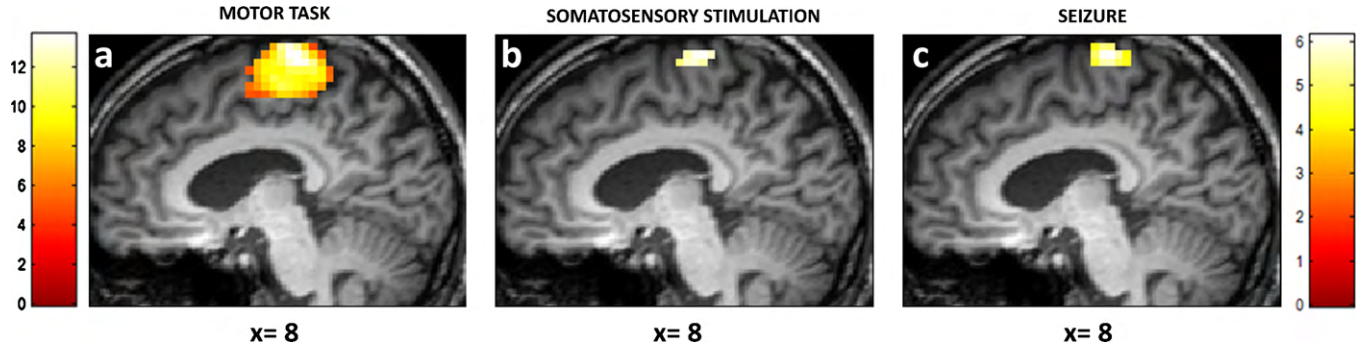

Fig. 3. fMRI results. (a) Functional map of the left foot motor area; block design; $p < 0.05$ corrected for multiple comparison; $k > 5$ voxels. (b) Functional map of the left foot somato-sensory cortex; event-related design; $p < 0.05$ corrected for multiple comparison; $k > 5$ voxels. (c) Functional map of three reflex seizures induced by left foot somato-sensory stimulation; event-related design; $p < 0.05$ corrected for multiple comparison; $k > 5$ voxels. Results are overlaid on the patient's T1 sagittal image ($x = 8$).[10]

5. Discussion

This case report demonstrates that: (1) patient's paroxysmal motor events were of epileptic origin; (2) there was a causal relationship between the intra-cortical plaque of the foot sensory-motor area and patient's seizures; (3) the focal motor status was the only manifestation of a MS relapse.

In particular, we utilize multimodal imaging techniques to study the BOLD correlates of reflex foot seizures and their relationships with physiological motor and somato-sensory functions. Indeed, few studies have focused on the BOLD correlates of ictal activity (owing to seizure unpredictability and the limitations of this technique), particularly in motor seizures, and even fewer have so clearly defined the relationship between the epileptogenic zone (pathological activation), normal functional anatomy (physiological activation) and structural lesion.

It is well known that cortical lesions constitute a substantial part of total lesion load in MS patients.[11,12] Despite this, few cases have clearly documented a causal relationship between a cortical lesion and seizures. Even more rare are descriptions of repeated seizures/status epilepticus due to a MS relapse. We were able to find only two case reports of 'epilepsia partialis continua' triggered by a new cortical inflammatory lesion involving the central region.[5,6] Accordingly to these reports, we considered the repeated seizures of the patient as event-related. That is secondary to the inflammatory lesion of the sensory-motor cortex. The question remains as to whether it was the lesion itself or the oedema accompanying the lesion that was responsible for the development of the seizures.[3] The intra-cortical plaque of the patient was small and non-enhancing. This implies that even a small inflammatory lesion if located in strategically brain regions (as it is the sensory-motor cortex) can cause seizures or status epilepticus.[4–6] The fact that the patient's lesion did not show contrast enhancement is consistent with the time lag elapsed between symptom onset and MR imaging. Indeed, the new brain MRI study was undertaken about 40 days after the onset of focal seizures. Unfortunately the patient was referred to our Hospital only when he developed a secondarily generalized tonic–clonic seizure. This time lag between symptom onset and MR imaging could explain the absence of contrast enhancement (gadolinium). This fact could also suggest that epileptogenesis developed after the acute phase of the inflammatory lesion.

Finally, seizures showed a poor response to a standard AED therapy for status epilepticus. On the contrary, seizures control was achieved after initiation of steroid treatment as for any other MS relapse. The same lack of efficacy of AEDs together with a positive response of intravenous steroid therapy was reported previously.[4–8] These case reports, therefore, underlie the importance to start soon an anti-inflammatory therapy when there is evidence that seizures are secondary to new cortical/subcortical MS lesions.

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Conflict of interest statement: None declared.

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